Successful treatment of SAPHO syndrome with apremilast

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Abstract: Synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome is a rare disease with inflammatory osteoarticular and skin involvement. The pathogenesis of SAPHO syndrome remains unclear, but evidence suggests it may be an autoinflammatory disease triggered upon exposure to infectious agents in genetically predisposed individuals. Induction of the IL-23/Th17 axis as well as neutrophil activation seem to play a key role, and therapies targeting these immunological pathways, including TNF-inhibitors, ustekinumab, secukinumab and the IL-1 inhibitor anakinra are potential treatment options that need further investigation. Here we report a case of a 24-year-old woman suffering from SAPHO syndrome who presented at our clinic with palmoplantar pustulosis and sternoclavicular joint involvement. Previous treatments with topical steroids and keratolytics combined with NSAIDs, intravenous methylprednisolone, methotrexate and salazopyrin had all failed to improve symptoms. Therapy with etanercept was not tolerated, and due to a previous demyelinating peripheral neuropathy, further treatment with TNF inhibitors was avoided. We initiated ustekinumab 45mg, which improved skin manifestations but not joint pain. Dose escalation to 90mg initially improved joint pain, but the dose had to be reduced to 45mg again due to increased infections. During subsequent 45mg ustekinumab treatment joint pain exacerbated so we switched to secukinumab, which improved skin and joint symptoms significantly but was associated with a pustular hypersensitivity reaction. Finally, we began treatment with apremilast, a pan-cytokine approach, resulting in stabilization of the skin and joint symptoms without side effects. To our knowledge, this is the first case report of apremilast as a treatment for SAPHO syndrome.

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Successful treatment of SAPHO syndrome with apremilast

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Keywords: SAPHO, biological, ustekinumab, secukinumab, apremilast

Abstract

Synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome is a rare disease with inflammatory osteoarticular and skin involvement. The pathogenesis of SAPHO syndrome remains unclear, but evidence suggests it may be an autoinflammatory disease triggered upon exposure to infectious agents in genetically predisposed individuals. Induction of the IL-23/Th17 axis as well as neutrophil activation seem to play a key role, and therapies targeting these immunological pathways, including TNF-inhibitors, ustekinumab, secukinumab and the IL-1 inhibitor anakinra are potential treatment options that need further investigation. Here we report a case of a 24-year-old woman suffering from SAPHO syndrome who presented at our clinic with palmoplantar pustulosis and sternoclavicular joint involvement. Previous treatments with topical steroids and keratolytics combined with NSAIDs, intravenous methylprednisolone, methotrexate and salazopyrin had all failed to improve symptoms. Therapy with etanercept was not tolerated, and due to a previous demyelinating peripheral neuropathy, further treatment with TNF inhibitors was avoided. We initiated ustekinumab 45mg, which improved skin manifestations but not joint pain. Dose escalation to 90mg initially improved joint pain, but the dose had to be reduced to 45mg again due to increased infections. During subsequent 45mg ustekinumab treatment joint pain exacerbated so we switched to secukinumab, which improved skin and joint symptoms significantly but was associated with a pustular hypersensitivity reaction. Finally, we began treatment with apremilast, a pan-cytokine approach, resulting in stabilization of the skin and joint symptoms without side effects. To our knowledge, this is the first case report of apremilast as a treatment for SAPHO syndrome.

What's already known about this topic?

- SAPHO syndrome is a disease of unknown cause but genetically several similarities to auto inflammatory diseases have been found. Clinically dermatological and osteoarticular manifestations resemble signs of neutrophil activation.

- Usual treatments include NSAIDs and corticosteroids but treatment with TNF-alpha or IL-1 antagonists has also been previously reported.

What does this study add?

- Given that TNF-alpha, IL-23 and IL-17 together with activated neutrophils are involved in the pathogenesis of SAPHO syndrome, blocking of these cytokines are potential strategies in treatment-refractory cases. As such, the use of specific cytokine-directed antibodies like ustekinumab or secukinumab or pan-cytokine inhibition with apremilast provide further therapeutic options in the management of this rare condition.

Introduction

SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis and osteitis) is a rare disease with inflammatory osteoarticular and skin involvement, the most common manifestations being palmoplantar pustulosis (PPP, up to 65% of cases) and acne (up to 39% of cases) together with inflammation of the axial and sternoclavicular joints [1].

Case report

A 24-year-old woman suffering from therapy-refractory SAPHO syndrome characterized by PPP and mainly sternoclavicular joint involvement was referred to our department. She reported intermittent severe pain of the right sternoclavicular joint and both shoulders. An MRI showed arthritis and osteitis of the right sternoclavicular joint, discrete arthritis in the lumbar vertebral bodies 2 / 5 and the left sacroiliac joint. Dermatological manifestations were plantar pustulosis with severe erythema and thick scaling, and palmar pustulosis with mild erythema and marked scaling. The maximal palmoplantar psoriasis area and severity index (PPPASI) was 31.2 (**Figure 1**). Additionally, new rapidly progressing nail-alterations occurred. CRP was mildly elevated (8.6 mg/L, reference <5) and erythrocyte sedimentation rate was normal (14 mm/h). The father of the patient was also diagnosed with SAPHO syndrome. Previous topical steroids and keratolytics combined with systemic therapies, including NSAIDs, weekly intravenous methylprednisolone, methotrexate and salazopyrin had all failed to improve symptoms. Etanercept 50mg weekly was begun but discontinued due to severe injection site reactions. Treatment options for the patient at that time were to switch to another TNF-alpha inhibitor (TNFi) or ustekinumab, as involvement of the IL-23/Th17 pathway in SAPHO syndrome has been suggested [2]. The latter was favored

because of a previously diagnosed demyelinating peripheral neuropathy. TNFi are contraindicated in multiple sclerosis and exacerbations or new onset demyelinating diseases have been reported during TNFi treatment. [3] The patient was treated with ustekinumab 45 mg at week 0, 8, 16 and then every 12 weeks. The second injection was delayed compared to the standard scheme due to gastrointestinal complaints, but physical examination, laboratory workup and gastroscopy remained unsuspicious. During treatment the PPPASI score improved dramatically but the treatment had no effect on joint pain, and additional treatment with NSAIDs and prednisone showed only little effect. The dose of ustekinumab was then increased to 90 mg every 12 weeks with initial significant improvement of joint pain. As the patient developed frequent upper airway infections, the dosage had to be reduced to 45 mg, which led to recurrence of joint pain and nail alterations. An MRI showed persistence of the inflammation of the right sternoclavicular joint, as well as new onset inflammation of the left sternoclavicular joint. Ustekinumab was thus discontinued and, as the peripheral neuropathy was completely asymptomatic, adalimumab was begun with the loading dose of 80 mg followed by 40 mg every other week beginning at week 1. Upon treatment with adalimumab, pustulosis and joint pain exacerbated with marked impairment of everyday activities. Adalimumab was stopped and secukinumab subsequently initiated due to its inhibition of the Th17 pathway and excellent activity in psoriasis and psoriatic arthritis [4]. Upon treatment with secukinumab, starting with 300 mg weekly over 4 weeks followed by 300 mg every 4 weeks, a marked improvement of the PPPASI score was observed including improvement of the nail alterations.

Four months after secukinumab initiation the patient developed a generalized pustular skin rash consistent with a drug hypersensitivity reaction. Secukinumab-specific T-cells were confirmed by lymphocyte transformation test. Secukinumab was discontinued and apremilast, which is approved for psoriasis and psoriatic arthritis, was started (standard induction scheme, followed by 30 mg twice daily). During the first four weeks the patient experienced common, usually intermittend side effects of apremilast such as headaches, diarrhea, nausea and vomiting, which thereafter resolved spontaneously. The clinical response of the skin lesions previously achieved with secukinumab was maintained under apremilast treatment at 7 months of follow-up, with a PPPASI of 2.4 (**Figure 2**) and no reported joint pain. Change in nail alterations could not be evaluated because of regularly applied artificial nails. At present the patient has been treated with apremilast 30 mg twice daily for 6 months achieving long lasting disease control without significant side effects. When the patient deviates from her treatment plan (apremilast 30mg, twice daily), she experiences increased itch with or without pustule formation which abate promptly when she returns to her regular dosing schedule. Recently the patient developed one episode of

intermittent severe headaches probably caused by the patients' intake irregularities which necessitated a transient reduction in dose (re-induction with one starter pack of apremilast).

Discussion

Here we present the case of a patient with therapy-refractory SAPHO syndrome successfully treated with apremilast. Treatments with biologics such as TNFi or anakinra have been reported in SAPHO syndrome, but only a few reported cases with ustekinumab exist and just recently a report with secukinumab has been published. Our patient showed disease remission induced by secukinumab and maintained through apremilast. As the patient gets flares when deviating from the treatment plan with apremilast, we assume that apremilast is suppressing the inflammation sufficiently.

The pathogenesis of SAPHO syndrome remains unclear, however several similarities to auto inflammatory diseases have been found. Genetic studies have associated SAPHO syndrome with mutations in LPIN2, NOD2 and PSTPIP1 and the HLA-B27, -39 and -61 alleles have been found more frequently in patients with SAPHO syndrome as compared to healthy individuals [6, 7]. Recently a multifactorial model where an autoimmune reaction is triggered by infectious agents in genetically predisposed individuals has been suggested [5]. Here pathogens – most importantly *Propionibacterium acnes* – have been associated with SAPHO syndrome in skin biopsies, with reports describing successful treatment with antibiotics. In addition, an upregulation of IL-8, IL-17, IL-18, TNF-alpha and IL-1 have been shown [8]. We did not find evidence of elevated serum cytokines (IL-1beta, IL-6, IL-8, IL-12, INF-gamma, TNF-alpha and soluble IL-2 receptor alpha) in our patient, but these investigations were done during treatment and no baseline levels were performed. There is still debate if chronic recurrent multifocal osteomyelitis (CRMO) belongs to the juvenile spectrum of SAPHO syndrome and how the latter can be conclusively differentiated from psoriatic arthritis, which rarely shows hyperostosis and osteitis [9].

Treatment options for SAPHO syndrome include NSAIDs, corticosteroids, antibiotics (doxycycline, azithromycin etc.), bisphosphonates, colchicine, methotrexate, sulfasalazine, TNFi, anakinra, surgery and recently also ustekinumab and secukinumab [7,10,11].

Palmoplantar pustular psoriasis with psoriatic arthritis is an important differential diagnosis for SAPHO syndrome. Osteitis and arthritis of the sternoclavicular joint rarely occur in psoriatic arthritis but are typical features of SAPHO syndrome, which were present in our patient. The cytokine profile of SAPHO syndrome was found to be similar to that of psoriasis [6], which together with the clinical similarities led to the introduction of well-established therapies like TNFi for treatment of SAPHO syndrome, with good symptom control in most cases [12]. Recently also ustekinumab and secukinumab

have shown efficacy in SAPHO syndrome with good response on skin manifestations but no improvement of joint involvement [2,10,11], which is a general issue with most therapies [7]. In contrast to the recently reported cases, our patient's skin manifestations responded well to ustekinumab and the joint pain improved after dose escalation. During secukinumab our patient also achieved good disease control with dramatic improvement of the PPPASI and joint pain.

IL-17 is a cytokine produced by Th17 cells, which were shown to be increased in patients suffering from SAPHO syndrome [8]. Since secukinumab had to be discontinued in our patient due to a hypersensitivity reaction with positive lymphocyte transformation test, we introduced a treatment with apremilast. Apremilast acts via its dialkoxyphenyl ring as a specific phosphodiesterase 4 (PDE-4) inhibitor and is non-selective for PDE-4 subtypes. Apremilast enhances intracellular cyclic adenosine monophosphate (cAMP) levels through protein kinase A (PKA) phosphorylation and activation, resulting in upregulation by cAMP responsive element binding protein (CREB) and down-regulation of NF-κB-dependent genes. Consequently, proinflammatory cytokine production of innate and adaptive immune cells is downregulated by apremilast. This leads to upregulation of immunomodulatory cytokines like IL-10 as well as downregulation of IFN-gamma, TNF-alpha and IL-23. The inhibition of PDE-4 skews the balance of cytokines towards an anti-inflammatory state, potentially leading to control of the inflammation.

In SAPHO syndrome, diverging responses to different targeted biologicals could reflect the involvement of separate proinflammatory pathways including IL-1, IL-17 and TNF-alpha, which may suggest further, as yet unrecognized, immunological subtypes of the disease. By treating our patient with apremilast, the suppression of pro-inflammatory cytokines such as TNF-α and IL-17 subsequently inhibitis the activation of both, T cells and neutrophils, a "pan-cytokine, multi-cell" immunomodulatory approach [13].

To our knowledge, this is the first case report of the successful treatment of SAPHO syndrome with apremilast; moreover, given the upregulation of the IL-23/IL-17 axis, the effectiveness of secukinumab, ustekinumab and apremilast introduce new therapeutic options for SAPHO syndrome and warrant further investigation.

Figure legends

Figure 1 a-c: Palmoplantar manifestation prior to ustekinumab treatment (month 0, PPPASI 31.2)

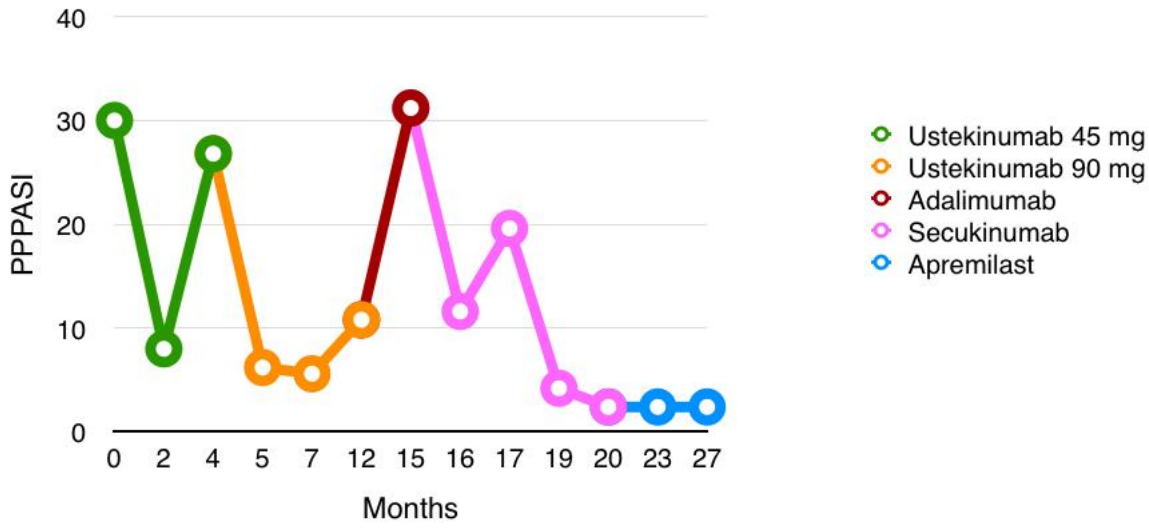
Figure 2 a-c: Palmoplantar manifestations during treatment with apremilast (month 23, PPPASI 2.4)

Figure 3: PPPASI (Palmoplantar Psoriasis Area and Severity Index) and treatments over time. Months since beginning of ustekinumab treatment.

Figure 1

Figure 2

Figure 3



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